THE DIVISION OF INTRAMURAL RESEARCH

NAEHS COUNCIL REPORT

FEBRUARY 2001

DIR Recruitments
February 2001

Scientific Director
A national search has been reopened to fill the position of Director, Division of Intramural Research, NIEHS. This individual serves as Scientific Director and directs laboratory and clinical research through 18 Laboratories and Branches with approximately 1100 government employees and contract personnel and an annual budget of approximately 140 million dollars. The Scientific Director is the principal advisor to the Institute Director on scientific affairs involving multidisciplinary biomedical research programs. Candidates are currently being considered for interviews.

Chief, Laboratory of Pulmonary Pathobiology
A national search for a new Chief of the Laboratory of Pulmonary Pathobiology (LPP) is taking place. The LPP is engaged in research on the biology of the respiratory tract system at the cellular, biochemical and molecular level to develop a better understanding of pathogenetic mechanisms involved in development of airway diseases. The search committee, Chaired by Dr. Perry Blackshear (Clinical Director), has recommended a candidate and negotiations are in the final stages.

Staff Scientist-Veterinary Pathologist
The Laboratory of Environmental Pathology is seeking a highly motivated Toxicologic Pathologist experienced in rodent toxicology and carcinogenicity studies to work within the National Toxicology Program (NTP). The successful candidate will be involved primarily in the management and oversight of the pathology peer review (evaluation) and interpretation and reporting of the data. Also the candidate will be expected to identify and pursue special projects that will advance the understanding of various biological endpoints. The search committee, chaired by Dr. Gary Boorman (National Toxicology Program), is reviewing applications.

Tenure-Track Neuroscientist
The Division of Intramural Research is recruiting for a tenure-track neuroscientist to conduct independent research that will complement or expand ongoing activities in neuropharmacology, neuroimmunology, signal transduction, synaptic plasticity, reproductive and developmental toxicology and neurotoxicology. Dr. Jean Harry, Laboratory of Toxicology, chairs the search committee. Interviews have been completed and the final recommendation is expected shortly.

Staff Scientist-Knockout Core Facility Manager
The Laboratory of Reproductive and Developmental Toxicology is recruiting a Staff Scientist with expertise in mouse molecular genetics or a related discipline to serve as the Head of the Transgenic Knockout Core Facility. The successful applicant will generate mutant mice using embryonic stem cell technologies, plan and provide scientific oversight in the conduct of targeting vector design, and serve as a resource expert on mouse genetics and embryology. The search committee, chaired by Dr. Mitch Eddy (Laboratory of Reproductive and Developmental Toxicology), has recommended a candidate to the Scientific Director.

Staff Scientist-NMR Chemist
The Laboratory of Structural Biology is seeking a chemist to serve as the technical expert for the preparation and structural analysis of isotopically labeled proteins using Nuclear Magnetic

Resonance (NMR) techniques. Experience in multidimensional NMR techniques as well as the design, preparation, isolation, purification and concentration of biological macromolecules is essential. The search committee, chaired by Dr. Elizabeth Murphy (Laboratory of Signal Transduction), has recommended a candidate to the Scientific Director.

Tenure-Track Epidemiologist

A national search is being conducted for a tenure-track investigator who will develop an independent research program in noncancer chronic disease epidemiology, with emphasis on the potential environmental causes of neurological diseases and dysfunctions in humans such as Parkinson's disease, Alzheimer's disease and multiple sclerosis. Individuals with the ability to integrate basic and molecular biology, genetics, toxicology, exposure assessment and epidemiology are sought. The Search Committee, chaired by Dr. Clarice Weinberg (Chief, Biostatistics Branch), is selecting candidates to interview.

New Appointments in the Division of Intramural Research

Dr. Michelle Hooth

Dr. Michelle Hooth was recently recruited for a Staff Scientist position in the General Toxicology Group, Toxicology Operations Branch, Environmental Toxicology Program DIR. Dr. Hooth received her Ph.D. in Toxicology as well as postdoctoral training from the University of North Carolina at Chapel Hill. She also completed postdoctoral training in the Environmental Carcinogenesis Division, National Health and Environmental Effects Research Laboratory, USEPA. Her research background is in carcinogenesis.

Dr. Hooth will manage contract toxicological studies on chemicals and will serve as an expert resource on the toxicology and carcinogenicity of these compounds. Her responsibilities include designing animal studies to evaluate the toxicity and carcinogenicity of chemicals selected by the NTP and the evaluation and interpretation of toxicity and carcinogenicity data for publication as NTP technical reports and papers in scientific journals.

Recent Publications:

Hooth, M. J., DeAngelo, A. B., George, M. H., Gaillard, E. T., Travlos, G. S., Boorman, G. A., and Wolf, D. C. (2000) Subchronic sodium chlorate exposure in drinking water results in a concentration-dependent increase in rat thyroid cell hyperplasia. *Toxicologic Pathology*, in press.

Golubovskaya, V. M., Filatov, L. V., Behe, C. I., Presnell, S. C., Hooth, M. J., Smith, G. J., and Kaufmann, W. K. (1999) Telomere shortening, telomerase expression, and chromosome instability in rat hepatic epithelial stem-like cells. *Molecular Carcinogenesis*, 24:209-217.

Hooth, M. J., Coleman, W. B., Presnell, S. C., Borchert, K. M., Grisham, J. W., and Smith, G. J. (1998) Spontaneous neoplastic transformation of WB-F344 rat liver epithelial cells. *The American Journal of Pathology*, 153:1913-1921.

Presnell, S. C., Hooth, M. J., Borchert, K. M., Coleman, W. B., Grisham, J. W., and Smith, G. J. (1998) Establishment of a functional hepatocyte growth factor/c-met autocrine loop in spontaneous transformants of WB-F344 rat liver stem-like cells. *Hepatology*, 28:1253-1259.

Hooth, M. J., Vincent, J. L., Coleman, W. B., Presnell, S. C., Grisham, J. W., and Smith, G. J. (1998) Genomic fluidity is a necessary event preceding the acquisition of tumorigenicity during spontaneous neoplastic transformation of WB-F344 rat liver epithelial cells. *Hepatology*, 28:78-85.

Golubovskaya, V. M., Presnell, S. C., Hooth, M. J., Smith, G. J., and Kaufmann, W. K. (1997) Expression of telomerase in normal and malignant rat hepatic epithelia. *Oncogene* 14: 1233-1240.

Training and Mentoring

The Fellows Award for Research Excellence-2001

The Fellows Award for Research Excellence (FARE) was started in 1995 to recognize scientific excellence among NIH intramural trainees. Trainees submit an abstract of their research, which is peer reviewed in a blinded study section competition. The awards are funded by the Scientific Directors, the Office of Research on Women's Health, and the Office of Education. In 2000, 639 applications were received and 159 (25%) were funded with $1000 travel awards to attend a meeting in the United States at which they presented their abstract, either as a poster or a seminar. FARE 2001 winners will be invited also to present their work at one of the FARE poster sessions that will follow each of the Wednesday Afternoon Lecture Seminars in Bethesda, and to serve as a judge for FARE 2002.

The NIEHS had 14 winners of FARE 2000 awards:

Winner	*Laboratory/Branch*	*Mentor*	*Abstract Title*
Dr. Arti Patel	Laboratory of Molecular Carcinogenesis	Theodora Devereux	Hypermethylation of p16Ink4a in mouse lung tumor cell lines and primary mouse adenocarcinomas
Dr. Alberto Inga	Laboratory of Molecular Genetics	Dr. Michael Resnick	Novel p53 mutants exhibiting enhanced transcriptional activation and altered promoter selectivity are revealed using a yeast-base functional assay
Dr. Andrew Wallace	Laboratory of Signal Transduction	Dr. John Cidlowski	Proteasome inhibition abrogates ligand dependent downregulation and enhances transcriptional activity of the glucocorticoid receptor
Dr. Dipak Mahato	Laboratory of Reproductive and Developmental Toxicology	Dr. Kenneth Korach	Elucidating the mechanisms of estrogen action on the male reproductive tract by germ cell transplantation
Ms. Christine Parks	Epidemiology Branch	Dr. Glinda Cooper	Crystalline silica and risk of systemic lupus erythematosus (SLE): a population-based case-control study in the southeastern United States
Dr. Polina Shcherbakova	Laboratory of Molecular Genetics	Dr. Thomas Kunkel	Inactivation of DNA mismatch repair by increased expression of yeast MLH1
Dr. Se-Te Huang	Laboratory of Signal Transduction	Dr. James Putney	BCL-2 phosphorylation status modulates glucocorticoid action in t-lymphocytes

Dr. Bin Liu	Laboratory of Pharmacology and Chemistry	Dr. Jau-Shyong Hong	Development of an inflammation-induced rodent model for Parkinson's disease and discovery of a novel agent for potential therapeutic intervention of Parkinson's disease
Dr. Diana Pettit	Laboratory of Signal Transduction	Dr. Jerrell Yakel	Beta-amyloid peptide directly modulates nicotinic receptors in the hippocampal slice
Dr. Seung Joon Baek	Laboratory of Molecular Carcinogenesis	Dr. Thomas Eling	Expression of NSAID activated gene, NAG-1, is associated with NSAID-induced apoptosis
Dr. James Caffrey	Laboratory of Signal Transduction	Dr. Stephen Shears	Metabolic functions of diphosphorylated inositol phosphates in yeast
Dr. Lisa Broad	Laboratory of Signal Transduction	Dr. James Putney	The role of (1,4,5)IP3 and the (1,4,5)IP3-receptor in regulating capacitive calcium entry
Dr. Franz-Joseph Braun	Laboratory of Signal Transduction	Dr. James Putney	Single channel recording of endogenous store-operated channels
Dr. Jenelle Martinez	Laboratory of Computational Biology and Risk Analysis	Dr. Nigel Walker	Comparative TCDD dose responses from human lung peripheral epithelial cell lines

Awards and Honors in the Division of Intramural Research
February 2001

Dr. Tom Darden (Laboratory of Structural Biology) was the keynote speaker at the Third International Workshop for Methods for Macromolecular Modeling held in October in New York.

Dr. Darlene Dixon (Laboratory of Experimental Pathology) was selected Chair of Toxicology (SOT) Continuing Education (CE) Committee, 2001-2002.

Dr. Jan Drake (Chief, Laboratory of Molecular Genetics) presented the keynote address at the Timofeeff-Ressovsky Centennial Conference, Dubna, Russia on September 9, 2000 where he also received the Biosphere and Mankind Medal.

Dr. Ruth Little (Epidemiology Branch) was awarded a Benjamin Meaker Visiting Professorship in the Department of Child Health at the University of Bristol, England. She is also currently an invited visiting scientist at the International Agency for Research on Cancer, an Institute of WHO, in Lyon, France.

Dr. Chris Portier (Acting Director, Environmental Toxicology Program) received the Outstanding Risk Practitioner of the Year award from the Society for Risk Assessment.

Dr. Dale Sandler (Epidemiology Branch) began her term as President of the American College of Epidemiology.

Dr. Richard Sharp (Office of the Scientific Director) started his term as Public Policy Scholar at the Woodrow Wilson Center in Washington, D.C.

Dr. Shephen Shears (Laboratory of Signal Transduction) was awarded an "Iwatare Scholarship" by Kyushu University Station for Collaborative Research in Fukuoka, Japan.

Dr. Ray Tennant (Chief, Laboratory of Environmental Carcinogenesis and Mutagenesis) gave the Herbert M. Parker Lecture at the Hanford Symposium on October 20, 2000.

Dr. Clarice Weinberg (Chief, Biostatistics Branch) has been invited to speak at a plenary session of the joint meeting of the Society for Epidemiologic Research, the Canadian Society for Epidemiology and Biostatistics, the American College of Epidemiology and the Epidemiology Section of the American Public Health Association at the Epidemiology Congress meeting in Toronto in June 2001.

Dr. Allen Wilcox (Chief, Epidemiology Branch) received the Herman A. Tyroler Distinguished Alumni Award from the University of North Carolina Department of Epidemiology and delivered the annual Tyroler Lecture at UNC in November 2000. Dr. Wilcox also received an award from the Norwegian Medical Research Council that includes a professorship at the University of Bergen. He will begin his term as the Editor-in-Chief of *Epidemiology* beginning in March 2001.

Dr. Sam Wilson (Laboratory of Structural Biology) was the keynote speaker at the Midwest DNA Repair Meeting in Indianapolis, Indiana in June 2001. He began a one-year term as a member of the ASBMB Council and he also chaired the Mammalian DNA Repair Gordon Research Conference.

Technology Transfer Activity for FY 2000

Material Transfer Agreements

Material Transfer Agreements (MTAs) reflect cooperative research between the NIEHS and the non-NIH research community. An MTA not only allows exchange of research material (e.g., cell lines, transgenic mice) but also allows for protection of NIEHS intellectual scientific property, inventions, licenses, and publication rights of scientists. In FY 2000, the NIEHS Office of Technology Transfer (Dr. John S. Penta, Technology Transfer Coordinator) reviewed and approved 224 MTA agreements, of which 85% were with academic institutions and the remainder with pharmaceutical and biotechnology commercial organizations. Last year the NIEHS participated in 180 MTAs, and with 224 this past year the increase is 25%.

Employee Invention Reports

Seven Employee Invention Reports (EIRs) or EIR actions were reviewed and approved by Dr. John Penta, the NIEHS Technology Development Coordinator. Following review and recommendation by the NIEHS Technology Evaluation Advisory Committee, chaired by Dr. David Armstrong (Laboratory of Signal Transduction), and/or the NIEHS Scientific Director, the following approved EIRs were submitted to the U.S. Patent Trademark Office for patent action by the NIH Office of Technology Transfer on behalf of the NIEHS in FY 2000:

Name of Invention	*NIEHS Inventor*	*Laboratory/Branch*
Gamma-glutamyl Transpepidase Inhibitor	Dr. Robert London	Laboratory of Structural Biology
Non-steroidal anti-inflammatory drug-related gene, NRG-1	Dr. Thomas Eling.	Laboratory of Molecular Carcinogenesis
Identification of compounds that potentiate the activity of muscarinic potassium channels	Dr. David Armstrong	Laboratory of Signal Transduction
Methods for the identification of textual and physical structure query fragments for the analysis of text and biopolymer information	Dr. Robert Boissy	Laboratory of Computational Biology and Risk Analysis

Cooperative Research and Development Agreements

Three Cooperative Research and Development Agreements (CRADAs) were initiated or activated with commercial organizations on behalf of NIEHS scientists:

Optimization of TAR Cloning, Gennaissance Pharmaceuticals, Drs. J. Carl Barrett (Laboratory of Molecular Carcinogenesis) and Vladimir Larianov (Gene Isolation Unit).

Functional Analyses of Bone Morphogenic Proteins (BMPs) During Neural Tissue Induction, Neural Tissue Development, and Neural Patterning, Riken Brain Science Institute (Japan), Dr. Yuji Mishina (Laboratory of Reproductive and Developmental Toxicology).

Zinc Finger DNA Binding Proteins, Sangamo BioSciences, Inc., Dr. Trevor Archer (Laboratory of Reproductive and Developmental Toxicology).

Consultations with NIEHS Scientists

The Technology Development Coordinator was asked to consult with DIR scientists on more than 150 occasions on issues relating to technology transfer took place between Dr. Penta and NIEHS scientists. Advice provided included employee inventions, publications, data ownership and cooperative research with nongovernment organizations in the U.S. (pharmaceutical and biotechnology companies).

International Activities in the Division of Intramural Research
FY 2000

Dr. Cynthia Afshari (Laboratory of Molecular Carcinogenesis) is collaborating with Dr. Mitsuo Oshimura, Tottori University in Japan, to identify and study the function of senescence genes and imprinting genes; with Dr. Markus Kiechle, GSF-National Research Center for Environment and Health, Neuherberg, Germany, to examine the effects of low dose irradiation in yeast models, and with Dr. P. Andrew Futreal, Sanger Center, Cambridge, UK, to study the function of breast cancer susceptibility genes.

Dr. Steven Akiyama (Laboratory of Molecular Carcinogenesis) has a long-term collaboration with scientists at the University of Kyoto, Japan, to identify and characterize novel cytoskeleton proteins important for tumor cell adhesion. He has also served as grant reviewer for the Italian Ministry for University and Research; for the Welcome Trust, London, U.K.; the British Columbia Health Research Foundation, Canada; and the Human Frontiers of Science Program, Strasbourg, France.

Dr. Trevor Archer (Laboratory of Reproductive and Developmental Toxicology) collaborated with Dr. D. Rodenhiser and colleagues at the University of Western Ontario, Canada, on a project examining the role of DNA methylation on the expression of the BRCA1 gene in breast cancer cells.

Dr. Dave Armstrong (Laboratory of Signal Transduction) is collaborating with Professor Anton Hermann, Department of Molecular Neurobiology and Cellular Physiology from the Institute of Zoology, University of Salzburg, Hellbrunnerstr, Austria, on a pilot project involving K channel regulation by oxidative stress. This work was conducted at the NIEHS for a one-month period and is projected to result in an ongoing collaboration.

Dr. Douglas Bell (Laboratory of Computational Biology and Risk Analysis) was involved in planning of the US-European Workshop on Gene-Environment Interaction: Research at the Interface of Toxicology and Epidemiology to be held in Munich, September 2001.

Dr. Perry Blackshear (Director, Office of Clinical Research) is collaborating with scientists at Oxford Glycosciences, Abingdon, UK, to apply proteomics approaches to protein glycation in diabetes, as markers of disease control and complications; with Dr. Nahum Sonenberg, McGill University, Montreal, Canada, on genetic modifiers of insulin action involving PHAS-I knockout mice; with George Kolias, Institute of Immunology, Biomedical Sciences Research Center 'Alexander Fleming', Vari, Greece, on interactions between TTP knockout mice and their various TNF and TNF receptor knockout and knockin lines; with Dr. Matthias Gaestel, Institute of Clinical Biochemistry and Pathobiochemistry, Medical University Clinic, Wuerzburg, Germany, on P38 kinase – TTP interactions using TTP knockout mice; with Dr. Brigitte Kaissling, University of Zurich, Switzerland, on interstitial cell MARCKS and MLP expression in the normal kidney and in kidneys of mice with fibroproliferative diseases; with Dr. Georgia Panopoulous, University of Berlin, Germany, on Xenopus/Amphioxus on EST collections and cross-hybridizations; with Dr. Willems Luc, Department of Applied Biochemistry and Biology, Faculty of Agronomy, Gembloux, Belgium, on interactions between bovine leukemia virus, HTLV and TTP in the pathogenesis of bovine leukemia; with Dr. Marion V. Squiers, Dept. of Pathology, The Radcliffe Infirmary, Oxford, England, on MARCKS and MLP in lissencephaly syndromes; with Dr. Orly Reiner, Department of Molecular Genetics, The Weizmann Institute of Science, Rehovot, Israel, on MARCKS and MLP in animal models of lissencephaly

syndromes; and with Dr. M. J. Harris, Department of Medical Genetics, University of British Columbia, Vancouver, British Columbia, Canada, on the mapping of neural tube defect susceptibility genes and their modifiers.

Dr. James Bonner (Laboratory of Pulmonary Pathobiology) initiated a new collaborative initiative with Dr. Alvaro R. Osornio-Vargas, Chief of the Department of Outdoor Health at the University of Mexico City, to identify components of air pollution particulates that cause adverse respiratory effects. He was also the co-organizer and co-chair of a session on the role of cytokines in lung fibrosis at the International Colloquium on Pulmonary Fibrosis held in Stockholm, Sweden.

Dr. John Bucher (Toxicology Operations Branch) along with Dr. Joe Roycroft and Dr. Ron Melnick have been involved in discussions with the consortium of European Researchers headed by Dr. Clemens Dasenbrock of the Fraunhofer Institute, Hannover, Germany, who are performing a series of rodent cancer studies examining radiofrequencies involved in cellular telephone transmissions. The consortium is planning their initial studies and is receiving funding from the European Union and the cell phone manufacturers. They have provided design advice and have explored options for participating in their studies.

Dr. Raj Chhabra (Toxicology Operations Branch) was invited by the World Health Organization to serve as a member of the Seventh Review Board on Concise International Chemical Assessment Documents, which met in Helsinki, Finland in June 2000.

Dr. John Cidlowski (Chief, Laboratory of Signal Transduction) served on the organizing committee for the International Congress of Endocrinology. He also spoke at the International Congress for Flow Cytometry as well as publishing papers with a group in England.

Dr. Tom Darden (Laboratory of Structural Biology) collaborated with Dr. Kholmirzo Kholmurodov, a scientist from Tazahkistan currently employed at the RIKEN High Performance Computing Center in Japan.

Dr. Jan Drake (Chief, Laboratory of Molecular Genetics) served on the Executive Board of the International Genetics Federation (IGF), which oversees the International Congresses of Genetics. He was also co-organizer of the Timofeeff-Ressovsky Centinnial Conference held in Dubna, Russia, September 6-9,2000. Timofeeff-Ressovsky was a founder of molecular biology, a leading geneticist, and the founder of radiation ecology in the USSR.

Dr. Mitch Eddy (Laboratory of Reproductive and Developmental Toxicology) has a collaboration with Dr. Chisato Mori of Chiba University School of Medicine in Chiba, Japan. They determined that at least three mRNA splice variants are expressed at specific stages of germ cell development and that these are produced by alternative use of three exons and use of unique exon splice sites. This research began while Dr. Mori was a Visiting Scientist in LRDT, NIEHS. Dr. Eddy also collaborated with Dr. Hideo Gotoh at the National Institute of Animal Health in Tsukuba, Japan on the identification of proteins associated with recombination hot spots and their roles during meiotic recombination in pachytene spermatocytes; with Dr. Patricia Cuasnicu from the Inst. Biol. Med. Experimental, Buenos Aires, Argentina preparing to produce mice with a knockout of a gene expressed specifically in the epididymis that is involved in epididymal maturation. Dr. Eddy serves as member of the Advisory Committee, Japanese Testis Workshop and as an ad hoc reviewer of research grants for funding agencies in Australia, Italy and Canada.

Dr. Dori Germolec (Laboratory of Toxicology) co-organized a meeting on the Epidemiology of Occupational and Environmental Factors Associated with Autoimmunity sponsored by the

IPCS of the WHO and held in Bilthoven, the Netherlands May 2001 and serves as a member of the WHO task force established to facilitate the collaborations and to seek funding for research in this area. She also has a collaborative study with Dr. Jeff Vos at the RIVM in the Netherlands to examine the effects of in utero exposure to hexachlorobenzene in the Sprague-Dawley rat.

Dr. Beth Gladen and Dr. Ruth Little (Biostatistics Branch) collaborated with scientists from several institutions in Kyiv, Ukraine (Institute of Pediatrics, Obstetrics and Gynecology; National Medical University; Kyiv Medical Academy of Post-Diploma Education) on pilot work to evaluate the possibility of studying the relationship of environmental pollutants to reproductive health in Ukraine. In addition, they are using data previously collected by Health Canada, Ottawa, Ontario, Canada to examine patterns of exposure to organochlorines, including a number of insecticides and PCB congeners in a national sample of breast milk.

Dr. Joyce Goldstein (Laboratory of Pharmacology and Chemistry) participated in a study of the relative importance of two polymorphic P450s in metabolism of an anticonvulsant drug mephenytoin in humans with Dr. J. A. Kato and Dr. Yasumori of Japan. Another collaboration involved a study with Dr. J. O. Miners of Australia on the importance of CYP2C9 in metabolizing a new diuretic agent used in man. She is also an invited lecturer to the Denmark Benzon Symposium, an international symposium of current topics in medicine.

Dr. Joe Haseman (Biostatistics Branch) has participated in an OECD validation exercise for the uterotrophic assay with 20 labs from around the world. Each lab provided individual animal uterus weight data for animals subjected to various test substances.

Dr. James Huff (Office of the Scientific Director) presented an invited talk on breast cancer risks from environmental chemicals at the Collegium Ramazzini in Carpi, Italy in October 99; a sponsored lecture in Copenhagen, Denmark in May 2000; and an invited lecture at the 5th International Symposium on Predictive Oncology and Therapy in Geneva, Switzerland, October 2000.

Dr. Anton Jetten (Acting Chief, Laboratory of Pulmonary Pathobiology) has collaboration with Dr. J. P. de Villartay, the Directeur de Recherche at the Hospital Necker-Engants Malades, Paris, France on the role of ROR-gamma in thymocyte maturation.

Dr. Larry Lazarus (Laboratory of Computational Biology and Risk Analysis) was the plenary lecturer at the Annual Conference on Opioid Mimetic Analgesics at Kobe Gakuin University in Kobe Japan in March 2000 and at the 120th Annual Meeting of the Pharmaceutical Society of Japan, in Gifu, Japan March 28-31, 2000.

Dr. Matthew Longnecker (Epidemiology Branch) participated in a collaborative project on the comparison of polychlorinated biphenyl levels across studies of human neurodevelopment. Other countries participating in the project are Denmark, Canada, Netherlands and Germany. He also collaborated on a research project with the National Institute of Public Health in Cuernavaca, Mexico on the effect of the antiandrogen DDE on anthropometric measures at birth. Dr. Longnecker reviewed applications for establishment of MRS Research Unites for the Medical Research Council of South Africa in Cape Town, South Africa and grant proposals for the Northern Contaminants Program Canada in Hull, Canada.

Dr. Robert Maronpot (Chief, Laboratory of Environmental Pathology) served as a special expert to the Safety Working Group of the International Cooperation on Harmonization of

Technical Requirements for Registration of Veterinary Medicinal Products at the invitation of the U. S. Food and Drug Administration. The charge of the group was to develop international guidelines for the safety testing of veterinary drug residues in human food. Separate guidelines are being developed for genetic toxicity, reproductive toxicity, subacute and chronic toxicity, and carcinogenicity. Meetings were held in Brussels in October 1999 and Tokyo in April 2000.

Dr. James Mason (Laboratory of Molecular Genetics) has collaborations with Dr. Mikhail Golubovsky, Russian Academy of Sciences, St. Petersburg, Russia, to work on a project characterizing telomere-telomere interactions in *Drosophila* and with Dr. Maurizio Gatti, University of Rome, Italy, to characterize a mutation in *Drosophila* that causes telomeric repeat arrays to grow to great lengths.

Dr. David Miller (Laboratory of Pharmacology and Chemistry) has collaborative projects with Dr. Rosalinda Masereeuw and Dr. Frans Russel of the Department of Pharmacology and Toxicology, University of Neijmegen, The Netherlands, on the regulation of xenobiotic excretion in renal proximal tubule by endothelin; and with Dr. Gert Fricker, Institute for Pharmaceutical Biotechnology, University of Heidelberg, Germany investigating the mechanism of xenobiotic transport in brain, focusing on brain capillaries and choroid plexus.

Dr. Yuji Mishina (Laboratory of Reproductive and Developmental Toxicology) collaborated with Drs. Masaharu Ogawa and Masahisa Ogawa of the Brain Science Institute, RIKEN, Saitama, Japan to uncover the function of BMP signaling for brain function.

Ms. Retha Newbold (Laboratory of Toxicology) is collaborating with Dr. Silvia Migliaccio, University of Rome, on a study on the effects of environmental estrogens on development of bone tissue and with Drs. Manfred Metzler and Savine Kulling, University of Karlsruhe, Germany, on a study on the effects of genistein and daidzein on the developing reproductive tract.

Dr. John O'Bryan (Laboratory of Signal Transduction) has collaborations with Dr. Peter McPherson of the Montreal Neurological Institute in Montreal, Quebec, Canada, on the role of intersectin adaptor protein in regulation of signal transduction pathways; and with Drs. Romke Bron and Janet Winter at the Novartis Institute for Medical Sciences in London, England, on the role of the ShcC adaptor protein in regulation of receptor tyrosine kinase signaling in primary neuron cultures.

Dr. Shayamal Peddada (Biostatistics Branch) will participate in the third meeting of the Organization for Economic Cooperation and Development in Paris, France

Dr. John Pritchard (Chief, Laboratory of Pharmacology and Chemistry) continues his collaboration on xenobiotic transport and elimination with Dr. Natascha Wolff of the Department of Physiology at the University of Goettingen in Goettingen, Germany.

Dr. Jim Putney (Laboratory of Signal Transduction) collaborated with Dr. Tomohiro Kurosake of Kansai University, Moriguchi, Japan to study the role of IP3 receptors in capacitative calcium entry, a mechanism of calcium entry into cells that is linked to phospholipase C activation in a variety of cell types.

Dr. Ghanta Rao (Laboratory of Experimental Pathology) completed a collaborative project with RIVM of the Netherlands entitled "Phenolic Phytoprotectants – Role in Preventing Initiation and Progression of Cancer" using transgenic animal models. The results of this project are expected to be published soon.

Dr. Walter Rogan (Epidemiology Branch) collaborated with colleagues from Taichung and Tainan, Taiwan on the faculty of the National Cheng Kung University on psychiatric and developmental follow-up of children transplacentally exposed to PCBs.

Dr. Roel M. Schaaper (Laboratory of Molecular Genetics) has a collaboration with Dr. Iwona J. Fijalkowska, Institute of Biochemistry and Biophysics, Polish Academy of Sciences, Warsaw, to investigate the fidelity of leading and lagging strand DNA replication in the bacterium *E. coli*; with Drs. Youri I. Pavlov and Stanislav G. Kozmin, Department of Genetics, Saint Petersburg State University, Saint Petersburg, Russia, on a study to investigate mechanisms underlying the toxic and mutagenic effects of base analog mutagens (supported by a NATO Collaborative Research Grant0; and with Dr. Kazuo Negishi, Gene Research Center, Okayama University, Okayama, Japan, to characterize the role of DNA mismatch repair in protecting cells against the mutagenic consequences of base analog mutagens.

Dr. Tina Teng (Laboratory of Reproductive and Developmental Toxicology) served on the organizing committee of the 5th International Conference on Lactoferrin to be held in Alberta Canada May 4-9, 2001.

Dr. Kenneth Tomer (Laboratory of Structural Biology) continued his ongoing collaboration with Professor Michael Przybylski of Konstanz University in Germany and Professor Ferenc Hudecz of Eotvos Loarant University, Hungarian Academy of Sciences, Budapest, Hungary on the application of mass spectrometry to biological problems, especially epitope mapping by mass spectrometry.

Dr. Allen Wilcox (Chief, Epidemiology Branch) collaborated with Dr. Rolv Terje Lie and the Norwegian Medical Birth Registry looking at the statistics of fathers who have malformations having well-formed babies. The Norwegian Registry is a unique resource that links medical and birth records through personal identifiers.

Dr. Roger Wiseman (Laboratory of Women's Health) has a series of collaborative research studies with Dr. Peter Soderkvist's laboratory at Linkoping University in Sweden to define molecular genetic alterations that give rise to chemically induced lymphomas in mice.

HIGHLIGHTS FROM THE NATIONAL TOXICOLOGY PROGRAM
February 2001

- Drs. Christopher J. Portier, John R. Bucher and J. Richard Hailey, NIEHS, are meeting with representatives from the Cancer Research Center of the European Ramazzini Foundation of Oncology and Environmental Sciences Commission on February 6-8, 2001 in Bologna, Italy. The goal of this meeting is to discuss the capability and feasibility for a collaborative toxicology and carcinogenesis research program between the two institutes.

- At the behest of the US Congress, the NIEHS initiated contact with scientists designated by the Government of Vietnam to discuss the development of a joint, collaborative research program on the health and environmental effects of Agent Orange (AO) and its principal toxic contaminant, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (dioxin) in Vietnam. Dr. Olden, Director of the NIEHS, led a US delegation to Singapore November 27-December 1, 2000 to meet with a delegation from Vietnam to discuss procedures, priorities, and potential problems associated with initiating a joint research program. The US delegation included senior scientists from NIEHS, EPA, CDC, and NIH's Fogarty International Center. The Vietnamese delegation was headed by Dr. Pham Khoi Nguyen, Vice Minister of the Ministry of Science, Technology and the Environment (MOSTE) and included scientists from MOSTE, the National Environment Institute, National Center for Natural Science and Technology, Ministry of Public Health, Hanoi Medical University, Ho Chi Minh City University of Medicine and Pharmacy, and Vietnam-Russia Tropical Research Center. Discussions focused on three areas of joint cooperation: human health effects, effects on the environment, and capacity building for dioxin research in Vietnam and identified key activities in each area that can be pursued. These include workshops in Vietnam for sharing current knowledge about the health effects of dioxins, areas of health concern for initial focus, analytical laboratory support for research efforts, pilot projects to evaluate novel remediation methods, and scientist exchange. Plans for workshops and scientist exchanges are being pursued, and it is anticipated that an additional planning session and a workshop will be completed in this fiscal year.

- In response to a nomination from the FDA, the NTP is currently evaluating the feasibility of performing rodent studies on the radio frequencies used in cellular telephone transmissions for potential carcinogenic effects. Because of the technical complexity of such studies, NTP staff is initially working with radio-frequency experts from the National Institute of Standards and Technology on an in-depth evaluation of studies either planned or underway to answer this question. The studies being evaluated are being carried out by a consortium of European investigators under the auspices of the European Union and by investigators at the Cancer Research Center of the European Ramazzini Foundation of Oncology and Environmental Sciences Commission. Following a careful assessment of these planned and ongoing studies, the NTP will determine whether a need exists to perform another independent evaluation to address this important public health concern.

- The NIEHS is providing support to the World Health Organization for the preparation of a manual, *Management and Communication of Environmental Risks*, that focuses on the management and communication of environmental risks. It will provide resources and

guidance for effective communication and management to those persons involved in the public-health decision making process. The manual will be designed as a resource for explaining the "why and how" of risk communication, an important issue when dealing with issues of public health concern such as environmental exposure to chemical and physical agents. It is intended to provide information for helping to achieve open, credible and trustworthy solutions to environmental issues. It will be designed for many audiences, but especially applicable as a risk communication tool for government agencies involved in such activities.

· Researchers (Drs. Christopher Portier, Nigel Walker, Amy Kim, Fred Parham, and Michael Kohn) from the Laboratory of Computational Biology and Risk Analysis, NIEHS were involved during 2000 with working with the EPA in rewriting the Dose-Response Modeling chapter for the EPA's health reassessment of dioxin. This chapter is one of the first occasions where extensive dose-response information on mechanistic, noncancer, and cancer endpoints has been analyzed together using the latest EPA benchmark dose approach to provide quantitative information on which regulatory decisions can be made regarding exposure to environmental agents. The entire dioxin reassessment including this chapter has undergone peer review by several groups, and its completion and release are anticipated sometime in 2001.

NTP Chemical Nomination and Selection

The NTP openly solicits nominations of chemicals and substances for study and receives nominations from a variety of groups including Federal agencies, public, industry, and labor unions. The NTP welcomes public comments on nominations and information from toxicology and carcinogenesis studies, as well as supplementary data on current production levels, human exposure, use patterns, or environmental occurrence. Nominations for NTP studies undergo several levels of review before toxicological studies are designed and implemented. The following nominated chemicals and substances completed the review process in 2000 and attention is being given for their study by the NTP: 1-Bromopropane and 2-Bromopropane, Chitosan, DNA-based products, Juglone, Potassium ferricyanide, and Radio-frequency radiation emissions of wireless communication devices.

NTP Board of Scientific Counselors Report on Carcinogens Subcommittee

The Report on Carcinogens (RoC) is a Congressionally mandated listing of "known human carcinogens" and "reasonably anticipated human carcinogens." The Secretary, Department of Health and Human Services, delegates its preparation to the NTP. The scientific review of nominated agents, substances, mixtures, or exposure circumstances involves three separate reviews (NIEHS/NTP Review Group, Interagency Working Group, and NTP Board of Scientific Counselors RoC Subcommittee) followed by review and comment by the NTP Executive Committee. Public comments are solicited multiple times during the process and are provided to each review group as available. The NTP Director receives the input from all reviews plus the public comments and makes his recommendations on the nominations to the Secretary, DHHS for review and approval. Information about the RoC is available on the NTP web site: http://ntp-server.niehs.nih.gov.

The NTP Board of Scientific Counselors Report on Carcinogens Subcommittee (RoC Subcommittee) met December 13-15, 2000 in Washington, DC to review the second set of nominations to the 10th RoC. This group for possible listing or upgrading the current listing include: chloramphenicol; metallic nickel & certain nickel alloys; methyleugenol; steroidal estrogens; talc (non-asbestiform) and talc (containing asbestiform fibers); trichloroethylene; broad spectrum UV radiation, and UVA, UVB, and UVC; and wood dust. Recommendation from this group and the two previous reviews will now go out for public comment. Additional information including background documents and public comments are available on the NTP web site.

NTP Board of Scientific Counselors Technical Reports Review Subcommittee

The NTP conducts research studies that are designed to characterize and evaluate the toxicologic potential, including carcinogenic activity, of selected chemicals in laboratory animals (usually two species, rats and mice). Chemicals selected for NTP toxicology and carcinogenesis studies are chosen primarily on the basis of human exposure, level of production, and chemical structure. The NTP Board of Scientific Counselors Technical Reports Review Subcommittee evaluates the results from the studies in an open, peer-review meeting. The next meeting of the Subcommittee is scheduled for May 3, 2001 at the NIEHS. The candidate reports scheduled for consideration at this meeting are acrylonitrile, citral, methacrylonitrile, *o*-nitrotoluene, and *p*-nitrotoluene. The Subcommittee is also tentatively scheduled to review a second set in October 2001.

Centers

NTP Center for the Evaluation of Risks to Human Reproduction (CERHR)

The CERHR provides scientifically based assessments of the evidence for reproductive and developmental toxicity of man-made or naturally occurring chemicals or chemical mixtures. The first evaluation by the Center was a review of phthalates. Phthalates were chosen based on their high production volume, extent of human exposures, use in children's products, and/or published evidence of reproductive or development toxicity. A 16-member expert panel met three times over approximately a year to evaluate seven phthalate esters [butyl benzyl phthalate, di(2-ethylhexyl) phthalate: DEHP, di-isodecyl phthalate, di-isononyl phthalate, di-n-butyl phthalate, di-n-hexyl phthalate, and di-n-octyl phthalate]. The expert panel generally expressed "minimal " or "negligible" concern for the possibility that these substances may cause adverse reproductive effects under current levels of human exposure. The panel expressed serious concern about DEHP as used to make polyvinyl chloride medical tubing and other medical devices for feeding and medicating critically ill newborn infants and for assisting their breathing. Such procedures might result in exposures to DEHP much higher than for the general population and could affect development of the male reproductive system. The expert panel reports are available on the CERHR web site (http://cerhr.niehs.nih.gov). The NTP solicited public comment on the expert panel reports and is now reviewing the body of input for preparation of its Center Report. The Center Report will be transmitted to Federal and state agencies, interested stakeholders, and the public.

The next chemical planned for evaluation by the Center is methanol (CAS No. 67-56-1). An expert panel meeting is tentatively scheduled for April 18-20, 2001 at the Radisson Hotel Old Town, Alexandria, VA. A large toxicity database exists on the reproductive and developmental effects of methanol. Methanol is a commercially important, high production volume chemical (10.54 billion pounds, US production, 1993), with potential for occupational, consumer, and environmental exposure. It is used occupationally in chemical syntheses and as an industrial solvent. It is found in a variety of consumer products such as paints, antifreeze, cleaning solutions, and adhesives and is a by-product of sewage treatment, fermentation, and paper production. Because of methanol's current use in racecar fuels, there is potential for future, expanded use as a vehicle fuel or fuel additive.

NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM)

The NICEATM (established in 1998) and the Interagency Coordinating Committee on the Validation of Alternative Toxicological Methods (ICCVAM, established in 1997) collaborate to develop, validate, and achieve regulatory acceptance of new and improved test methods. On December 19, 2000, the ICCVAM Authorization Act (PL 106-545) established ICCVAM as a permanent committee of the NIEHS under NICEATM. ICCVAM will consist of the heads of 15 federal agencies or their designees (ATSDR, CPSC, Departments of Agriculture, Defense, Energy, Interior, and Transportation, EPA, FDA, NIOSH, NIH, NCI, NIEHS, NLM, and OSHA). The purposes of ICCVAM are to 1) increase efficiency and effectiveness of federal agency test method review; 2) eliminate unnecessary duplicative efforts and share experiences between federal regulatory agencies; 3) optimize utilization of scientific expertise outside the

federal government; 4) ensure that new and revised test methods are validated to meet the needs of federal agencies; and 5) reduce, refine, or replace the use of animals in testing, where feasible. The law establishes a Scientific Advisory Committee and requires agencies to determine that alternative test methods are valid.

The NTP Advisory Committee on Alternative Toxicological Methods (ACATM) for NICEATM met November 28, 2000 at the National Library of Medicine, Bethesda, MD. The Committee discussed recent ICCVAM/NICEATM test method meetings and proposed future activities. Meeting minutes will be posted on the ICCVAM/NICEATM web site: (http://iccvam.niehs.nih.gov). ACATM is composed of representatives from academia, industry, public interest organizations, other State and Federal agencies, and the international community. The Committee functions to provide advice on the activities and priorities of the NICEATM and ICCVAM and on ways to foster partnership activities and productive interactions among all stakeholders.

Recent ICCVAM/NICEATM Meetings

International Workshop on In Vitro Methods for Assessing Acute System Toxicity
The goal of this workshop, held October 17-20, 2000 in Arlington, VA, was to assess the current status of *in vitro* test methods for evaluating the acute systemic toxicity potential of chemicals and to make recommendations for validation efforts necessary for characterizing the usefulness and limitations of existing methods. A workshop report will be posted on the ICCVAM/NICEATM web site in the future.

Alternative Toxicological Methods for the New Millennium: Science and Application
The NIEHS and Department of Defense co-sponsored this symposium November 28-December 1, 2000 in Bethesda, MD. The latest issues, research, and trends toward addressing the reduction, refinement, and replacement of research animal use were discussed. The proceedings from this symposium will be published in the future.

Local Lymph Node Assay (LLNA) Workshop
ICCVAM in partnership with the ILSI Health and Environmental Sciences Institute organized a training workshop on the LLNA January 25-26, 2001 at the NIH. The objective of the workshop was to assist participants in gaining an understanding of the theory and application of the method. Additional information about the workshop is available on the ICCVAM/NICEATM web site. LLNA is used for assessing allergic contact dermatitis and was the first alternative test method to be reviewed using the ICCVAM process and has received regulatory acceptance from EPA, OSHA, and FDA.

Future Test Method Activities

Endocrine Distruptor Screening and Testing Program

At the request of EPA, ICCVAM and NICEATM are planning an Independent Peer Review Panel meeting to assess the validation status of several *in vitro* assays for use in EPA's Endocrine Disruptor Screening Program. In preparation for this meeting, NICEATM is preparing background review documents on *in vitro* estrogen receptor and androgen receptor binding and transcriptional activation assays. These documents will provide comprehensive reviews of available data and related information necessary for evaluating the validation status of these assays.

Workshops and Conferences

Safety Assessment of Genetically Modified Foods

The general public and the scientific community are increasingly concerned regarding the potential toxicity of genetically modified (GM) foods. Of specific interest is the ability of GM proteins to elicit potentially harmful immunologic responses including hypersensitivity and/or autoimmunity. The lack of information on the potential toxicity of these products has created a considerable backlash against the producers and users of these crops. To address these issues, the NTP along with the EPA and FDA is sponsoring a workshop, *Safety Assessment of GM foods*, to be held on September 24-26, 2001 in Research Triangle Park, NC. The goals of this meeting are to examine the current state of knowledge in this area, identify the critical issues regarding GM materials, and develop testing strategies for examining the toxicity of these compounds. Participants will include experts in food allergy, GM crops, and the regulatory aspects of these products. Additional information can be obtained by contacting Dr. Dori Germolec, NIEHS at (919) 541-3230 or germolec@niehs.nih.gov.

8th U.S.-Japan Workshop on Health Impacts of Global Change

The National Science Foundation, NIH, NIEHS, and the National Institute for Environmental Studies in Tsukuba, Japan sponsored a workshop on global change and human health, November 13-15, 2000 in Bethesda, MD. Dr. Warren Piver, NIEHS, served on the organizing committee. The workshop had two major themes: 1) Health impacts of exposure to higher temperatures and air pollutants and 2) health effects of stratospheric ozone depletion. The workshop emphasized the need for multi-disciplinary, multi-national, and integrated research activities that could provide quantitative estimates of the impacts of global change on human health. Attendance was broad including government research agencies and academic institutions in the United States and Japan. A report from the workshop is being prepared. Follow-up meetings between the United States and Japan are planned for developing collaborative research proposals that target studying health impacts from increasing temperatures interacting with air pollutants (March 2001) and from exposure to UV radiation (summer 2001).

The NTP continues to work toward increasing public outreach about its programs and activities. The NTP participated with an exhibit at the 128th Annual American Public Health Association Meeting and Exposition, *Eliminating Health Disparities*, November 12-16, 2000 in Boston, MA. This meeting attracted approximately 13,000 public health professionals interested in public health and public health policy. The NTP is scheduled to have an exhibit at the 40th Annual Meeting of the Society of Toxicology, March 25-29, 2001 in San Francisco, CA.